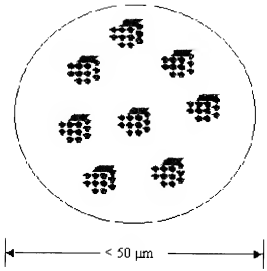
conventional processes it is estimated that only about 10 to 20% of an active agent reaches the lung because of losses to the device used to deliver the agent, loss to the mouth and throat, and loss due to exhalation. *See* specification at page 1, lines 17-20. Such losses lead to undesirable variable therapeutic agent levels and poor therapeutic control. *See* specification at page 1, lines 20-21. Moreover, deposition of the agent to the mouth and throat can lead to systemic absorption and undesirable side effects. *See* page 1, lines 21-22, of the application.

The claimed invention utilizes nanoparticulate active agent particles having average diameters of 1000 nm or less and having one or more surface stabilizers adsorbed to the surface of the active agent particles, as shown below:

< 1000 nm

The stabilized nanoparticulate active agent particles are dispersed in a liquid continuous phase, such as water. This type of formulation is known as a colloidal dispersion. In the claimed invention, the liquid dispersions are aerosolized to produce fine (i.e., less than 50 μm diameter) liquid droplets of the colloidal dispersion.

An exemplary droplet of an aerosol containing a nanoparticulate active agent is represented graphically below:



Prior to the present invention, nanoparticulate formulations were known. *See e.g.*, U.S. Pat. No. 5,145,684, cited by the Examiner. However, it was not known that such nanoparticulate formulations could be incorporated into aerosol formulations, much less any that could be delivered to a mammal's lung as discovered and claimed by the present invention.

The claimed invention satisfies a need in the art for aerosol compositions that can deliver a poorly soluble active agent to the lungs, a need which is not met by prior disclosures. Moreover, the claimed invention is not described or suggested in the cited prior art.

III. THE OFFICE ACTION

A. Informalities

The Examiner requested a copy of the IDS filed on August 31, 2000, together with references A4 and A6 cited therein. In response, Applicants enclose the requested copies, and note that the document number for A4 on the IDS is corrected to read "92/08446" instead of "08446."

B. Rejection of Claims under 35 U.S.C. § 112, Second Paragraph

Claims 28 – 45 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite on several grounds. Office Action at page 2-3. First, the Examiner considers that the reference to liquid droplets of one size and particles of another size in claim 28 is unclear. Second, the Examiner questions the origin of "crystalline agent" in claim 28. Finally, the Examiner challenges the use of the terms "comprising" and "comprises" [sic] in claim 28 because such terms allegedly fail to exclude unrecited claim elements. To the extent that this rejection may apply to claim 28, as amended, Applicants respectfully traverse this rejection.

1. The Claimed Droplets and Active Agent Particles are Well-Defined

Claim 28, as amended, defines clearly the relation between aerosol droplets and nanoparticulate therapeutic agent particles. The claim now recites only "liquid droplets," thereby removing any uncertainty caused by also reciting the singular form of the phrase. The claimed method employs aerosol droplets measuring less than about 50 microns in diameter. Each aerosol droplet, in turn, incorporates nanoparticulate therapeutic agent particles having an average diameter of less than about 1000 nm. Applicants submit that no confusion exists as to the difference between the liquid droplets, therapeutic agent particles, and their respective sizes.

2. Amendment of Claim 28 to Recite a "Therapeutic Agent"

To more particularly point out the claimed invention, claim 28, as amended, recites "therapeutic agent" instead of the allegedly indefinite "crystalline agent."

3. Use of "Comprising" Does Not Render the Claims Indefinite

The claimed method recites that a nanoparticulate aerosol composition is administered to a mammal to deliver that composition to the mammal's lungs. The Examiner notes correctly that the term "comprising" in this context allows for additional steps, but falls short of specifying how this widely accepted transitional phrase triggers a rejection under section 112, second paragraph.

In both *Gottzein* and *Davis*, upon which the Examiner relies, the Board affirmed *prior art* rejections of claims employing the term "comprising," which did not exclude additional elements found in the prior art. In contrast, the present invention is not taught or suggested by the prior art. *Infra*. Consequently, Applicants are satisfied that claim 28 adequately and clearly circumscribes the subject matter to which they are entitled.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 28 – 45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement on two grounds. Office Action at pages 3-4. Specifically, the Examiner considers the claim limitation "liquid droplet" to lack support in the specification. The method steps in claim 28, the Examiner further argues, are not disclosed. Applicants respectfully traverse this rejection.

Claim 28, as amended, recites only "liquid droplets," for which several instances of enabling support are found in the specification. *See, e.g.,* specification at page 3, line 18 ("liquid droplets"); page 1, line 18 ("aqueous droplets"); page 2, line 26 ("droplets of an aqueous dispersion of nanoparticles").

Additionally, ample enabling support for the method of claim 28 can be found in the specification. *See* specification at page 1, lines 14 ("delivery of agents to the lung") and 23 ("respiratory drug delivery"); page 24, lines 5 – 15 (example showing delivery of an agent to a rabbit). Applicants therefore submit that the specification provides enabling support for the claimed invention. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

D. Obviousness-Type Double Patenting Rejection of Claims

Claims 28 – 45 stand rejected as being allegedly obvious over claims 24 – 30 of U.S. Pat. No. 6,254,922 in the context of nonstatutory double patenting. Office Action at page 4. Applicants respectfully defer a response to this rejection until the Examiner has indicated allowable subject matter in the present case.

E. **Rejection of Claims Under 35 U.S.C. § 103(a)**

Claims 28 – 45 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Pat. No. 5,747,001 to Wiedmann *et al.* ("Wiedmann") and U.S. Pat. No. 5,145,684 to Liversidge *et al.* ("Liversidge"). Office Action at pages 5-6. In support of this rejection, the Examiner points out that both references teach a composition "which embraces Applicant's claimed invention," relying in particular on Wiedmann who purportedly discloses the administration of an aerosol of a nanoparticulate active agent to the respiratory system. The Examiner concludes that it would have been obvious to an artisan of ordinary skill to prepare a nanoparticulate aerosol composition for delivery to the lung because "droplets and particles of less than 400 and 1000 nm are taught by [Wiedmann and Liversidge]." Applicants respectfully traverse this rejection.

1. **Wiedmann is not Available as a Prior Art Reference**

Applicants courteously draw the Examiner's attention to the fact that the effective filing date of the present application (February 24, 1995) and the filing date of commonly-assigned Wiedmann are identical. Consequently, Wiedmann is not available as prior art against the present application.

2. **Liversidge does not Teach or Suggest Aerosol Compositions of Nanoparticulate Active Agents**

Liversidge is directed to nanoparticulate active agent compositions, comprising a nanoparticulate active agent having a particle size of less than about 400 nm, and a surface stabilizer adsorbed onto the surface of the active agent. *See* Liversidge at col. 2, lines 38 – 43. Liversidge, however, does not teach or suggest aerosol compositions of nanoparticulate active agents or methods of administering the same. Therefore, because Wiedmann is not available as prior art and Liversidge does not teach or suggest the claimed invention, it would not have been obvious to one of ordinary skill in the art to arrive at the claimed invention given the cited references.

Moreover, one of ordinary skill in the art at the time the claimed invention was made would not have been motivated to make an aerosol composition comprising the nanoparticulate active agent composition of Liversidge for the following reasons.

3. Aerosolization can Produce Unpredictable and Inefficient Delivery of Poorly Soluble Particles

The delivery efficiency of poorly soluble active agents via aerosolization can be unpredictable and inefficient. For example, a study on the nebulization of the water-insoluble drug budesonide showed that minimal amounts of drug substance were aerosolized *in-vitro*. *See* Cameron et al., "Evaluation of Nebulizers for use in Neonatal Ventilator Circuits" *Crit. Care Med.*, *18*(8):866-870, 868 (1990) (EXHIBIT 1).

Furthermore, studies by Tiano have shown that nebulization of drug particles in the range of one to six microns (1000 to 6000 nm) in diameter (which are contained within the aerosolized water droplets) is very inefficient for air-jet nebulizers and essentially impossible for ultrasonic nebulizers. *See* Tiano, S. L., "Functionality Testing Used to Rationally Assess Performance of a Model Respiratory Solution or Suspension in a Nebulizer" *UMI Dissertation Services*, 1995, Chapter IV, pages 60-68 (EXHIBIT 2) (Page 65: "It was concluded that an ultrasonic nebulizer could not efficiently aerosolize a respiratory suspension since only the solvent and not the insoluble particles (representing drug) would potentially be delivered to a patient."; Page 68: "[F]or both [air-jet and ultrasonic] nebulizers . . . the majority of spheres (85-100%) in the original suspension did not leave the nebulizer.").[1]

Similar behavior has been observed for actual drug suspensions by Nikander et al. *See* Nikander et al., "The Conventional Ultrasonic Nebulizer Proved Inefficient in Nebulizing a Suspension" *J. Aerosol Med.*, 12(2), 47-53 (1999) (EXHIBIT 3).

4. The Prior Art Teaches that Aerosolization of a Poorly Soluble Active Agent Combined with a Surfactant (i.e., a Surface Modifier) is Difficult or Impossible

Tiano (EXHIBIT 2) teaches that "[a]ttempts to aerosolize model suspensions with an air-jet nebulizer in the absence of a surfactant resulted in about 85% of the particles remaining in the nebulizer. Upon addition of a surfactant the aerosolization

[1] Applicants will supplement this response shortly to furnish Tiano.

improved slightly, but still nearly 75% of the particles remained in the medicament reservoir." *See* Tiano at page 75. Attempts to aerosolize model suspensions in an ultrasonic nebulizer resulted in nearly 100% of the particles remaining in the device, regardless of whether or not a surfactant was present. *See* Tiano at pages 66 and 75.

Moreover, Tiano described how the presence of a surfactant "caused marked differences in the functional aerosol characteristics." Tiano at page 68. The presence of a surfactant resulted in decreasing the fine droplet fraction and producing a variable nebulized outlet rate. Tiano at page 68. Tiano concludes that "it was not likely that these characteristics would be acceptable from a formulation or clinical performance point of view." Tiano at page 68. This clearly teaches that the use of a surfactant in combination with an active agent is not desirable for aerosol lung delivery. This conclusion is supported by Tiano when she stated that "although surfactants are commonly found in oral pharmaceutical and inhalation [metered dose inhaler] formulations, their utility in a respiratory suspension intended for nebulization delivery may be limited." Tiano at page 73.

Finally, Tiano et al. stated that the *in vitro* findings related to the use of poorly soluble drug and a surfactant in an air-jet and ultrasonic nebulizer "would likely result in the majority of the dose being impacted in a patient's mouth and throat which would likely lead to coughing or swallowing of the aerosol dose. Consequently, minimal therapeutic efficacy would be anticipated." Tiano at page 73.

This disclosure clearly suggested that an poorly soluble drug/surfactant composition, such as that disclosed in Liversidge, is not suitable for respiratory delivery. Accordingly, given this disclosure, one of skill in the art at the time the claimed invention was made would not have been motivated to attempt to produce an aerosol for respiratory delivery in view of Liversidge.

Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

IV. CONCLUSION

Applicants courteously request reconsideration of this application in view of the amendments and foregoing remarks. Applicants submit that this application is now in condition for allowance and an early notice to that effect is respectfully solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Dec 2, 2002 By Michele M Simkin

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If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

MARKED UP VERSION SHOWING CHANGES MADE

28. (Amended) A method of delivering an aerosol to the lungs of a mammal comprising administering a nanoparticulate aerosol composition comprising [:

(a)] liquid [droplet] droplets having a particle size of less than about fifty microns in diameter[; and] , wherein

[(b)] the liquid droplets comprise:

[(i)] (a) a liquid,

[(ii)] (b) crystalline particles of a therapeutic agent which is poorly soluble in said liquid, wherein the crystalline particles have an average particle size of less than about 1000 nm; and

[(iii)] (c) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles[, wherein the crystalline agent/surface modifier particles have an average particle size of less than about 1000 nm].